Remarks

The Applicant respectfully requests entry of the foregoing amendments and reconsideration of the application in view of the amendment above and the remarks below.

Rejections under 35 U.S.C. 103

Claims 44, 47-61, 64-65, 67 and 71-80 were rejected under 35 U.S.C. 103(a) as being unpatentable over Geng et al. (J. of Chromatography A, 2000, Vol. 870) ("Geng") in view of Nelson et al. (1995 Ana. Chem.) ("Nelson"). Claims 44, 47-61, 64-65, 67 and 71-80 have been canceled in this amendment, and therefore this rejection is rendered moot. Applicant respectfully request that this rejection be withdrawn.

The Newly Added Claims Are Allowable

Applicant respectfully submits that the newly added claims are allowable in view of the art of record. The examiner has previously cited Geng, Zhao (PNAS, 1996, Vol. 93:4020-4024) ("Zhao"), and Nelson and used such references in rejections. None of these references, however, teach each and every limitation of independent claims 81 or 97. Additionally, it would not have been obvious to one of skill in the art to combine the teachings of Geng with those of Zhao or Nelson.

The examiner correctly notes that Geng teaches elements of the claims, but does not disclose the use of antibodies as binding agents. In particular, Geng does not disclose the use of antibodies (or any other binding agent) formulated to specifically bind one monitor peptide. To do so would destroy the functionality of Geng's approach, whose purpose is to detect large sets of peptides, not a specific peptide analyte. The analysis in Geng is not restricted to individual peptides.

The examiner notes that Zhao describes the binding of peptides from a single digested protein to a monoclonal antibody generated against the protein, an application termed "epitope mapping." Zhao, however, does not describe the use of such antibodies in conjunction with a stable isotope labeled version of a peptides to achieve quantitation of the peptide or target protein. Quantitation is not disclosed in Zhao because the motivation of Zhao is structural characterization of the protein (i.e., determination of the location in the protein sequence of the

binding epitope of an antibody), not measurement of the amount of the protein and particularly not its amount in a complex biological sample. Hence, measurement of protein amount is not an object of Zhao, and it would make no sense to add the step of exposing a stable isotope labeled version of a peptide to the antibody (as recited in independent claims 81 and 97).

Additionally, Zhao does not teach the use of antibodies to specifically bind peptides from the digest of a complex sample: there is no use of a complex biological sample in Zhao, only a digest of one protein. In particular Zhao shows that the proteolytic enzyme Lys-C produces 10 peptides from digestion of this protein (including 3 pairs of overlaps), of which 6 are visible in the MS spectrum - of these 6, two are selected by the Ab (i.e., 33% of the peptides bind to the Ab). The proteolytic enzyme Asp-N: produces 12 peptides (including many overlaps), of which 7 are visible in the MS spectrum - of these 7, two are bound by the Ab. The third example of immunoprecipitation uses a family of all overlapping peptides: in one case 7 of 15 are bound by the Ab, and in the second case 3 of 15 are bound. The fourth example (phage display) uses random hexapeptides and shows that the Ab bound 11 sequences related to but not identical to the corresponding part of the target protein. This result emphasizes the background (off-target) binding observed. Nothing disclosed by Zhao suggests that an antibody would specifically bind a peptide from a complex digest (i.e., a digest of a complex biological sample). A complex biological sample contains >1,000 proteins, each of which can generate on average 50-100 peptides upon digestion, and thus a complex digest can contain > 50,000 peptides. Zhao does not suggest that an antibody would bind to one of the 50,000 peptides.

The examiner notes that Nelson describes the use of antibodies to bind specific proteins from a biological sample for MS detection. Nelson, however, does not describe the digestion of a sample to yield peptides, or the exposing of digest peptides to antibodies - as recited in independent claims 81 and 97. Nelson's object is to enrich and characterize intact proteins present in a biological sample, using antibodies prepared against the intact proteins. To digest the proteins to peptides would destroy the functionality of Nelson's method. Thus, there is no motivation in modify Nelson's approach to digest the sample proteins to peptides, as recited by independent claims 81 and 97.

Thus, while each of the cited references discloses some of the elements of the invention, none discloses each and every element recited by the claims. Additionally, neither Zhao nor Nelson can be properly combined with Geng because in each case the functionality of the references would be destroyed. For example, because Geng is focused exclusively on global analysis of peptide digests and has no intention of pre-selecting specific protein analytes in advance, there is no motivation in Geng's approach to capture specific, pre-defined intact proteins as disclosed in Nelson. Similarly, to modify the method of Geng to include steps of Zhao would destroy the purpose of Geng (to detect large sets of peptides, not a specific peptide analyte). Thus, one of skill in the art would not modify Geng with either Zhao or Nelson. Additionally, in one embodiment, the present invention aims to measure specific, pre-defined analytes (distinct from the goal of Geng); it does so through use of monitor peptides detected in the digest of a biological sample (distinct from the process of Nelson); and it uses an internal standard to achieve quantitation (distinct from the goal of Zhao). None of these authors would achieve their expressed purposes by modifying the references to render the pending claims obvious in view of such references.

Accordingly, Applicant respectfully submits that independent claims 81 and 97 are allowable over the cited prior art. Additionally, Applicant respectfully submits that the claims that depend from independent claims 81 and 97 are allowable at least because of their dependence from independent claims 81 or 97.

Conclusion

All of the stated grounds of rejection have been overcome. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding rejections and that such rejections be withdrawn. Applicant believes that a full and complete response has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that further personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Director is hereby authorized to charge any appropriate fees under 37 CFR 1.16, 1.17, and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 50-1283.

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Respectfully submitted,
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